Serial #: 10/056,790
Reference #: EX02-004C

AMENDMENTS TO THE SPECIFICATION

Please amend the specification to read as follows:

Paragraph [0029]:

The term "RRP polypeptide" refers to a full-length RRP protein or a functionally active fragment or derivative thereof. A "functionally active" RRP fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type RRP protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of RRP proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Current Protocols in Protein Science (1998) Coligan et al., eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. For purposes herein, functionally active fragments also include those fragments that comprise one or more structural domains of an RRP, such as a protease or rhomboid domain or a binding domain. Catalytic and other domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2~~; http://pfam.wustl.edu~~). Methods for obtaining RRP polypeptides are also further described below. Preferred fragments are functionally active, domain-containing fragments sharing at least 80% sequence identity or similarity, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% sequence identity or similarity with a contiguous stretch of at least 25 amino acids, preferably at least 50 amino acids, more preferably at least 100 amino acids, and in some cases, the entire length of any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, and 46. In further preferred embodiments, the fragment comprises the entire rhomboid domain (PFAM 01694).

Paragraph [0040]:

Preferably, the RRP polypeptide nucleic acid, fragment, ortholog, or derivative thereof has at least 70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with RRP. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. As used herein, "percent (%)

sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410~~;~~ ~~http://blast.wustl.edu/blast/README.html~~) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

Paragraph [00132]:

RNA was extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/μl. Single stranded cDNA was then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA~~, http://www.appliedbiosystems.com/~~).

Paragraph [0042]:

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, Advances in Applied Mathematics 2:482-489; database: European Bioinformatics Institute ~~wwwz.ebi.ac.uk/bio.sub.—sw/~~; Smith and Waterman, 1981, J. of Molec.Biol., 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" ~~(www.psc.edu)~~ and references cited therein.; W.R.

Pearson, 1991, Gen mics 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: Atlas of Protein Sequences and Structure, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 Nucl. Acids Res. 14(6):6745-6763). The Smith-Waterman algorithm is used to search databases for sequences similar to a query sequence. Smith-Waterman uses dynamic programming to determine how an optimal alignment between the query sequence and a database sequence can be produced. This alignment is obtained by determining what transformations the query sequence would need to undergo to match the database sequence. Transformations include substituting one character for another and inserting or deleting a string of characters. A score is assigned for each character-to-character comparison--positive scores for exact matches and some substitutions, negative scores for other substitutions and insertions/deletions. The first character in an insertion or deletion gap is scored with a gap open penalty and subsequent characters are scored with a gap extension penalty. Scores are obtained from statistically-derived scoring matrices. The combination of transformations that results in the highest score is used to generate an alignment between the query sequence and database sequence. Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated the "Match" value reflects "sequence identity."